10/030,678

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 * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:47:34 ON 07 APR 2005

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 15:47:41 ON 07 APR 2005
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STRUCTURE FILE UPDATES:     6 APR 2005  HIGHEST RN 848027-68-9
DICTIONARY FILE UPDATES:    6 APR 2005  HIGHEST RN 848027-68-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

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*                                                                       *
* The CA roles and document type information have been removed from     *
* the IDE default display format and the ED field has been added,       *
* effective March 20, 2005.  A new display format, IDERL, is now        *
* available and contains the CA role and document type information.     *
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http://www.cas.org/ONLINE/DBSS/registryss.html

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L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1               STR
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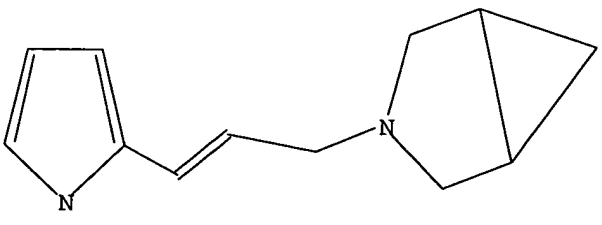


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FULL SEARCH INITIATED 15:47:57 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1204 TO ITERATE
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100.0% PROCESSED 1204 ITERATIONS 58 ANSWERS
SEARCH TIME: 00.00.01

L2 58 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 161.33 161.54

FILE 'CAPLUS' ENTERED AT 15:48:05 ON 07 APR 2005
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FILE COVERS 1907 - 7 Apr 2005 VOL 142 ISS 15
FILE LAST UPDATED: 6 Apr 2005 (20050406/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l2
L3 27 L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 27 DUP REM L3 (0 DUPLICATES REMOVED)

=> d l4 bib abs 1-27

L4 ANSWER 1 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:528499 CAPLUS
DN 141:220453
TI Enantioselective DNA Alkylation by a Pyrrole-Imidazole S-CBI Conjugate
AU Bando, Toshikazu; Narita, Akihiko; Asada, Ken; Ayame, Hirohito; Sugiyama, Hiroshi
CS Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto, 606-8501, Japan
SO Journal of the American Chemical Society (2004), 126(29), 8948-8955
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB Conjugates 12S and 12R of N-methylpyrrole (Py)-N-methylimidazole (Im) seven-ringed hairpin polyamide with both enantiomers of 1,2,9,9a-tetrahydrocyclopropa[1,2-c]benz[1,2-e]indol-4-one (CBI) were synthesized, and their DNA alkylating activity was examined High-resolution denaturing gel electrophoresis revealed that 12S selectively and efficiently alkylated at one match sequence, 5'-TGACCA-3', in 450-bp DNA fragments. The selectivity and efficiency of the DNA alkylation by 12S were higher than those of the corresponding cyclopropapyrroloindole (CPI) conjugate, 11. In sharp contrast, another enantiomer, 12R, showed very weak DNA alkylating activity. Product anal. of the synthetic decanucleotide confirmed that the alkylating activity of 12S was comparable with 11 and that 12S had a significantly higher reactivity than

12R. The enantioselective reactivity of 12S and 12R is assumed to be due to the location of the alkylating cyclopropane ring of the CBI unit in the minor groove of the DNA duplex. Since the CBI unit can be synthesized from com. available 1,3-naphthalenediol, the present results open up the possibility of large-scale synthesis of alkylating Py-Im polyamides for facilitating their use in future animal studies.

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:261245 CAPLUS
DN 140:333218
TI Sequence-Specific Gene Silencing in Mammalian Cells by Alkylating Pyrrole-Imidazole Polyamides
AU Shinohara, Kenichi; Narita, Akihiko; Oyoshi, Takanori; Bando, Toshikazu; Teraoka, Hirobumi; Sugiyama, Hiroshi
CS Department of Pathological Biochemistry, Medical Research Institute, Division of Biofunctional Molecules, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Chiyoda, Tokyo, 101-0062, Japan
SO Journal of the American Chemical Society (2004), 126(16), 5113-5118
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB Gene silencing was examined by sequence-specific alkylation of DNA by N-methylpyrrole (Py)-N-methylimidazole (Im) hairpin polyamides. Polyamides ImImPyPyγImImPyLDu86 (A) and ImImPyPyγImPyPyLDu86 (B) selectively alkylated the coding regions of the renilla and firefly luciferases, resp., according to the base pair recognition rule of Py-Im polyamides. Two different plasmids, encoding renilla luciferase and firefly luciferase, were used as vectors to examine the effect of alkylation on gene silencing. Transfection of the alkylated luciferase vectors-by polyamide A or B-into HeLa, 293, and NIH3T3 cells demonstrated that these sequence-specific DNA alkylations lead to selective silencing of gene expression. Next, the vectors were cotransfected into HeLa cells and the cells were treated with polyamide A or B. Selective reduction of luciferase activities was caused by both polyamides. On the basis of this sequence-specific alkylation and gene silencing activity, these alkylating Py-Im polyamides thus have potential as antitumor drugs to target specific gene expression in human cells.

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:158455 CAPLUS
DN 140:350153
TI C-H to N Substitution Dramatically Alters the Sequence-Specific DNA Alkylation, Cytotoxicity, and Expression of Human Cancer Cell Lines
AU Bando, Toshikazu; Narita, Akihiko; Iwai, Aki; Kihara, Kazunori; Sugiyama, Hiroshi
CS School of Biomedical Science, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan
SO Journal of the American Chemical Society (2004), 126(11), 3406-3407
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The authors designed and synthesized sequence-specific alkylating conjugates I and II, which selectively alkylate matched sequences at nanomolar concns. Conjugates I and II differ only in that the C-H is

substituted by an N in the second ring, which precisely recognizes and effectively alkylates DNA according to the recognition rule of Py-Im polyamides. The authors investigated sequence-specific DNA alkylation, cytotoxicity in 39 human cancer cell lines, and the effect on expression levels in cancer cell lines by Py-Im conjugates I and II. The COMPARE anal. of the mean graphs showed that conjugates I and II did not correlate well with each other (r = 0.65) despite having a common DNA alkylating mechanism (purine N3 alkylation). Array-based gene expression anal. demonstrated that there are several oppositely regulated genes. The results suggest the intriguing possibility that DNA alkylating agents recognizing longer base-pair sequences may provide a promising approach for developing new types of antigene agents.

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:406414 CAPLUS
DN 141:218281
TI Molecular design of effective sequence-specific DNA alkylating agents using pyrrole-imidazole polyamides
AU Bando, Toshikazu; Sugiyama, Hiroshi
CS Sch. Biomed. Sci., Tokyo Med. Dent. Univ., Japan
SO Seitai Zairyo Kogaku Kenkyusho Hokoku (Tokyo Ika Shika Daigaku) (2004), Volume Date 2003, 37, 49-55
CODEN: SZKHF9; ISSN: 1345-2886
PB Tokyo Ika Shika Daigaku Seitai Zairyo Kogaku Kenkyusho
DT Journal
LA English
AB New hairpin polyamide-CPI conjugates, compds. 12-14, were synthesized and their DNA alkylating activities compared with the previously prepared hairpin polyamide, compound 1, by high-resolution denaturing gel electrophoresis using 450-bp DNA fragments and by HPLC product anal. of the synthetic decanucleotide. In accord with our previous results, alkylation by compound 1 predominantly occurred at the G of the sequence 5'-AGTCAG-3' (site 3). In clear contrast, the hairpin CPI conjugate 13, which lacks one Py unit and possesses a vinyl linker relative to compound 1, efficiently alkylated the A of 5'-AGTCAG-3' (site 3) at nanomolar concns. The significantly different reactivity of the alkylating hairpin polyamides 1, 12, 13, and 14 was further confirmed by HPLC product anal. using a synthetic decanucleotide. The results suggest that the hairpin polyamide-CPI conjugate 13 efficiently alkylates according to Dervan's pairing rule, and with a new mode of recognition in which the Im-vinyl linker (L) pair targets the G-C base pairs. These results demonstrate that the incorporation of the vinyl linker pairing with Im dramatically improves the reactivity of the hairpin polyamide-CPI conjugates.

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:737733 CAPLUS
DN 139:276894
TI Preparation of hairpin-type pyrrole-imidazole polyamides as anticancer agents
IN Sugiyama, Hiroshi; Bando, Toshikazu; Saito, Isao
PA Japan Science and Technology Corporation, Japan
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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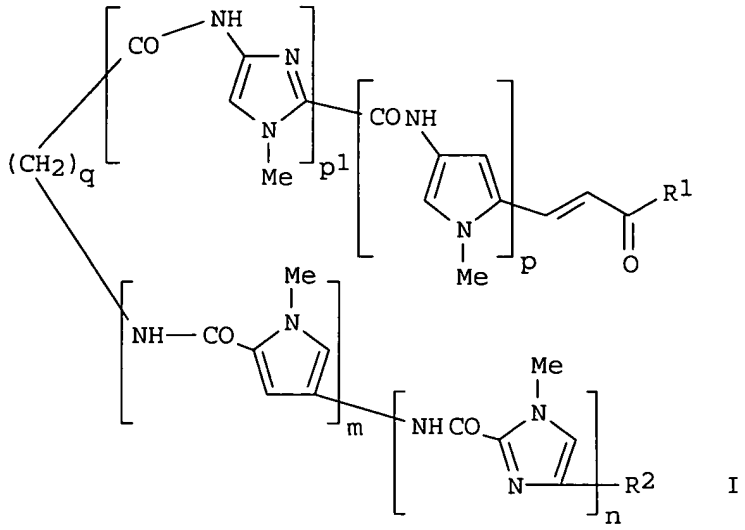
	W: US				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR				
	JP 2003261541	A2	20030919	JP 2002-63608	20020308
	EP 1491534	A1	20041229	EP 2003-707192	20030303

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK

PRAI JP 2002-63608 A 20020308
WO 2003-JP2423 W 20030303

OS MARPAT 139:276894

GI



I

AB It is intended to provide a pyrrole-imidazole polyamide type functional mol. having enhanced abilities of alkylating DNA and recognizing a sequence, compared with the existing functional mols. of this type, for a specific base sequence occurring on DNA. Hairpin polyamides have an alkylation site via a vinyl linker at the end of a pyrrole-imidazole polyamide and are represented by general formula (I; R1 = a site for alkylation reaction; R2 = H, alkyl, acetamido; p, p1, q, m, n = an integer). Disclosed are drugs for inhibiting the expression of a specific gene and anticancer agents containing the above hairpin polyamide. For example, I (m = p = p1 = 1, n = 2, q = 3, R1 = q) selectively alkylated A of the GTCA sequence of DNA (pUC-I'). The compds. I were tested for inhibiting the proliferation of various cancer cells.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:242708 CAPLUS
DN 138:315370
TI Inhibition of Transcription at a Coding Sequence by Alkylating Polyamide
AU Oyoshi, Takanori; Kawakami, Wakana; Narita, Akihiko; Bando, Toshikazu; Sugiyama, Hiroshi
CS Division of Biofunctional Molecules, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan
SO Journal of the American Chemical Society (2003), 125(16), 4752-4754
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB Transcription from DNA sequence-specifically alkylated by a hairpin polyamide (ImPyPy-γ-ImPyLDu86, 1) was investigated. High-resolution polyacrylamide gel electrophoresis demonstrated that conjugate 1 alkylated a 993-bp DNA fragment, in accordance with the Py-Im recognition rule, predominantly at the one match site on the GFP-encoding strand and at four sites (I'-IV') on the noncoding strand. Alkylation of DNA inhibited the formation of full-length mRNA and caused the transcription of truncated mRNA. Polyacrylamide gel electrophoresis demonstrated that the length of the truncated mRNA was consistent with the alkylated site on the coding

strand. Complete inhibition of full-length mRNA synthesis was observed in the presence of 50 nM 1. In clear contrast, the hydrolyzed derivative of 1, designated 2, produced no truncated mRNA, nor did it significantly retard transcription: >80% transcription of full-length mRNA was observed at 50 nM. These results clearly indicate that inhibition of transcription can be achieved with alkylating Py-Im polyamide even in the coding regions of genes.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:155388 CAPLUS
DN 138:333279
TI Highly Efficient Sequence-Specific DNA Interstrand Cross-Linking by Pyrrole/Imidazole CPI Conjugates
AU Bando, Toshikazu; Narita, Akihiko; Saito, Isao; Sugiyama, Hiroshi
CS Division of Biofunctional Molecules Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan
SO Journal of the American Chemical Society (2003), 125(12), 3471-3485
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
OS CASREACT 138:333279
AB We have developed a novel type of DNA interstrand crosslinking agent by synthesizing dimers of a pyrrole (Py)/imidazole (Im)-diamide-CPI conjugate, ImPyLDu86, connected using seven different linkers. The tetramethylene linker compound [I], efficiently produces DNA interstrand cross-links at the nine-base-pair sequence, 5'-PyGGC(T/A)GCCPu-3', only in the presence of a partner triamide, ImImPy. For efficient crosslinking by I with ImImPy, one A·T base pair between two recognition sites was required to accommodate the linker region. Elimination of the A·T base pair and insertion of an addnl. A·T base pair and substitution with a G·C base pair significantly reduced the degree of crosslinking. The sequence specificity of the interstrand crosslinking by I was also examined in the presence of various triamides. The presence of ImImIm slightly reduced the formation of a cross-linked product compared to ImImPy. The mismatch partners, ImPyPy and PyImPy, did not produce an interstrand cross-link product with I, whereas ImPyPy and PyImPy induced efficient alkylation at their matching site with I. The interstrand crosslinking abilities of I were further examined using denaturing PAGE with 5'-Texas Red-labeled 400- and 67-bp DNA fragments. The sequencing gel anal. of the 400-bp DNA fragment with ImImPy demonstrated that I alkylates several sites on the top and bottom strands, including one interstrand crosslinking match site, 5'-PyGGC(T/A)GCCPu-3'. To obtain direct evidence of interstrand cross-linkages on longer DNA fragments, a simple method using biotin-labeled complementary strands was developed, which produced a band corresponding to the interstrand cross-linked site on both top and bottom strands. Densitometric anal. indicated that the contribution of the interstrand cross-link in the observed alkylation bands was approx. 40%. This compound efficiently cross-linked both strands at the target sequence. The present system consisted of a 1:2 complex of the alkylating agent and its partner ImImPy and caused an interstrand crosslinking in a sequence-specific fashion according to the base-pair recognition rule of Py-Im polyamides.
RE.CNT 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:393696 CAPLUS
DN 139:358146
TI Specific alkylation of human telomere repeats by hairpin pyrrole-imidazole polyamide
AU Takahashi, Ryoko; Bando, Toshikazu; Sugiyama, Hiroshi
CS Institute of Biomaterials and Bioengineering, Division of Biofunctional Molecules, Tokyo Medical and Dental University, 2-3-10 Surugadai, Kanda, Chiyoda, Tokyo, 101-0062, Japan

SO Bioorganic & Medicinal Chemistry (2003), 11(12), 2503-2509
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
AB A novel hairpin polyamide-cyclopropapyrroloindole (CPI) conjugate PyImImIm-γ-PyPyPyLDu86 (conjugate 11), which targets human telomere repeats d(TTAGGG)n/d(CCCTAA)n, was synthesized. High resolution denaturing PAGE using 44 bp DNA fragments and HPLC product anal. of a synthetic nonanucleotide demonstrated that conjugate 11 alkylates the target adenine in the telomere repeats, 5'-CCCTAA-3'. Examination of the antitumor activity of conjugate 11 using a panel of 39 cancer cell lines demonstrated that the average concentration of conjugate 11 required for 50% growth inhibition was 5.75 μM, which is superior to pepleomycin and bleomycin and comparable to cisplatin.
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:690138 CAPLUS
DN 140:192333
TI Sequence Specificity, Reactivity, and Antitumor Activity of DNA-Alkylating Pyrrole-Imidazole Diamides
AU Bando, Toshikazu; Iida, Hirokazu; Tao, Zhi-Fu; Narita, Akihiko; Fukuda, Noboru; Yamori, Takao; Sugiyama, Hiroshi
CS Institute of Biomaterials and Bioengineering, Division of Biofuctional Molecules, Tokyo Medical and Dental University, Chiyoda-Ku, Tokyo, Kanda, 101-0062, Japan
SO Chemistry & Biology (2003), 10(8), 751-758
CODEN: CBOLE2; ISSN: 1074-5521
PB Cell Press
DT Journal
LA English
AB Three conjugates of imidazole (Im)-pyrrole (Py) diamide and a DNA-alkylating moiety derived from the antibiotic duocarmycin A were synthesized, and their sequence specificity, reactivity, and antitumor activity comparatively examined Sequencing gel anal. indicated that ImPyDu (1) alkylates DNA at the 3' end of AT-rich sequences at micromolar concentration ImPyDu86 (2) reacts with DNA at AT-rich sites together with dialkylation sites at micromolar concentration ImPyLDu86 (3) efficiently alkylates dialkylation sites at nanomolar concentration Average values of log IC50 against a 39 cancer cell line panel of 1-3 were -4.59, -5.95, and -8.25, resp. The differential growth inhibition pattern of 1-3 varied with relatively low correlation coeffs. Array-based gene expression monitoring was performed for 3 in a human lung cancer cell line. Substantial downregulation of expression was seen for genes involved in DNA damage response, transcription, and signal transduction.
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:840303 CAPLUS
DN 138:132742
TI Molecular design of a pyrrole - imidazole hairpin polyamides for effective DNA alkylation
AU Bando, Toshikazu; Narita, Akihiko; Saito, Isao; Sugiyama, Hiroshi
CS Division of Biofunctional Molecules Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan
SO Chemistry--A European Journal (2002), 8(20), 4781-4790
CODEN: CEUJED; ISSN: 0947-6539
PB Wiley-VCH Verlag GmbH & Co. KGaA
DT Journal
LA English
OS CASREACT 138:132742
AB New hairpin polyamide-CPI (CPI = cyclopropylpyrroloindole) conjugates, compds. 12-14, were synthesized and their DNA-alkylating activities compared with the previously prepared hairpin polyamide, compound 1, by

high-resolution denaturing gel electrophoresis with 450 base pair (bp) DNA fragments and by HPLC product anal. of the synthetic decanucleotide. In accord with our previous results, alkylation by compound 1 occurred predominantly at the G moiety of the sequence 5'-AGTCAG-3' (site 3). However, compound 12, in which the structure of the alkylating moiety of compound 1 is replaced with segment A of duocarmycin A DU-86 (CPI), did not show any DNA alkylating activity. In clear contrast, the hairpin CPI conjugate 13, which differs from compound 1 in that it lacks one Py unit and possesses a vinyl linker, alkylated the A of 5'-AGTCAG-3' (site 3) efficiently at nanomolar concns. Alkylation by compound 14, which has a vinyl linker, occurred at the A of 5'-AGTCCA-3' (site 6) and at several minor alkylation sites, including mismatch alkylation at A of 5'-TCACAA-3' (site 2). The significantly different reactivity of the alkylating hairpin polyamides 1, 12, 13, and 14 was further confirmed by HPLC product anal. by using a synthetic decanucleotide. The results suggest that hairpin polyamide-CPI conjugate 13 alkylates effectively according to Dervan's pairing rule, and with a new mode of recognition in which the Im-vinyl linker (L) pair targets G-C base pairs. These results demonstrate that incorporation of the vinyl-linker pairing with Im dramatically improves the reactivity of hairpin polyamide-CPI conjugates.
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:666652 CAPLUS
DN 138:85083
TI Sequence-specific protection of plasmid DNA from restriction endonuclease hydrolysis by pyrrole-imidazole-cyclopropapyrroloindole conjugates
AU Fujimoto, Kazuhisa; Iida, Hirokazu; Kawakami, Masako; Bando, Toshikazu; Tao, Zhi-Fu; Sugiyama, Hiroshi
CS Institute of Biomaterials and Bioengineering, Division of Biofunctional Molecules, Tokyo Medical and Dental University, Chiyoda, Tokyo, 101-0062, Japan
SO Nucleic Acids Research (2002), 30(17), 3748-3753
CODEN: NARHAD; ISSN: 0305-1048
PB Oxford University Press
DT Journal
LA English
AB The pyrrole-imidazole (Py-Im) triamide-cyclopropa pyrroloindole (CPI) conjugates ImPyImLDu86 (7) and ImImPyLDu86 (14) were synthesized and their alkylating activities and inhibitory effects on DNA hydrolysis by restriction endonucleases were examined Sequencing gel anal. demonstrated that conjugates 7 and 14 specifically alkylated DNA at 5'-CGCGCG-3' and 5'-PyGGCCPu-3', resp. Agarose gel electrophoresis indicated that incubation of a supercoiled plasmid, pSPORT I (4109 bp), with conjugate 7 effectively inhibited its hydrolysis by BssHII (5'-GCGCGC-3'), whereas conjugate 14 had no effect on this hydrolysis. These results suggest that conjugate 7 sequence-specifically inhibits the hydrolysis of DNA by BssHII. Sequence-specific alkylation by the Py-Im triamide-CPI conjugates was further confirmed by inhibition of the Eco52I (5'-CGGCCG-3') hydrolysis of conjugate 14-treated pQBI PGK (5387 bp). In clear contrast, hydrolysis of pQB1 PGK by DraI (3'-TTTAAA-3') was not inhibited by 5 μM conjugate 14. That ImImPy did not inhibit the hydrolysis of pQB1 PGK indicates that covalent bond formation is necessary for inhibition. A similar experiment, using linear pQBI PGK, achieved the same extent of protection of the DNA with approx. half the concentration of conjugate 14 as was required to protect supercoiled DNA from hydrolysis.
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:954878 CAPLUS
DN 139:30289
TI Regulation of gene expression by sequence-specific alkylating polyamide
AU Oyoshi, Takanori; Kawakami, Wakana; Bando, Toshikazu; Narita, Akihiko; Sugiyama, Hiroshi
CS Division of Biofunctional Molecules, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo, 101-0062,

Japan
SO Nucleic Acids Research Supplement (2002), 2(Twenty-ninth Symposium on Nucleic Acids Chemistry), 259-260
CODEN: NARSCE
PB Oxford University Press
DT Journal
LA English
AB In order to investigate the inhibition of gene expression by a new type of hairpin polyamide-CPI conjugate 1, its ability to inhibit transcription in cell free system was investigated. Sequence-selective alkylation of double-stranded DNA by 1 was investigated by denaturing gel electrophoresis using 1000 bp DNA fragment which codes for green fluorescence protein (GFP) under the control of T7 promoter. Anal. of DNA sequence indicated that 1 alkylated predominantly at the site of 5'-AGTCA-3' in coding region of GFP. The transcript by T7 RNA polymerase using the alkylated DNA as a template was analyzed by PAGE. The results clearly indicate that 1 inhibits transcription by alkylation of coding region at a nanomolar concentration
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:833321 CAPLUS
DN 135:371743
TI Preparation of pyrrole-imidazole polyamide-duocarmycin segment conjugates as interstrand crosslinking agents for DNA in cancer treatment
IN Sugiyama, Hiroshi; Bando, Toshikazu; Iida, Hirokazu; Saito, Isao
PA Japan Science and Technology Corporation, Japan
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001085733	A1	20011115	WO 2001-JP3756	20010501
	W: US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
	JP 2001322992	A2	20011120	JP 2000-140361	20000512
	EP 1281711	A1	20030205	EP 2001-926081	20010501
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PRAI	JP 2000-140361	A	20000512		
	WO 2001-JP3756	W	20010501		

OS MARPAT 135:371743
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. represented by the following general formula A-L-B-X-B-L-A (I; wherein B represents a chemical structure capable of recognizing a base sequence of a DNA; A represents a chemical structure capable of binding to one of the bases of the DNA; L represents a linker by which the chemical structures A and B can be linked to each other; and X represents a spacer by which the A-L-B components can be linked to each other), by which two DNA strands can be interstrand-crosslinked, are prepared Also claimed are a method of interstrand-crosslinking DNA by using these compds. and medicinal compns. containing interstrand crosslinking agents of DNA. In the compds. I, the above chemical structure capable of recognizing a base sequence of a DNA is derived from pyrrole and/or imidazole and the chemical structure capable of binding to one of the bases of the DNA possesses a cyclopropane ring. More specifically, the compds. represented by N-[3-[4-(N-methylimidazol-2-ylcarbonylamino)-N-methylpyrrol-2-

yl]acryloyl]cyclopropa[c]pyrrolo[3,2-e]indole derivs. (pyrrole-imidazole polyamide-duocarmycin segment conjugates) [II; X = CO, COCH:CHCO, CO(CH2)4CO, CO-p-C6H4-CO] are prepared The B component in the compds. I, i.e. the 4-(N-methylimidazol-2-ylcarbonylamino)-N-methylpyrrole moiety of II, recognizes a DNA base sequence and is capable of specifically interstrand-crosslinking to the specific base sequence of DNA. These compds. inhibit the replication of DNA by interstrand-crosslinking to DNA and thereby are useful for the treatment of cancer. Interstrand-crosslinking reaction of the compds. II to DNA oligomers was examined using polyacrylamide gel electrophoresis. For example, it was confirmed that II [X = CO(CH2)4CO] interstrand-crosslinked to the TGGC or GCCA or its complimentary sequence of DNA, in particular in the copresence of a triamide (III; X = Y = N and Z = CH; X = Y = Z = N; X = N and Y = Z = CH; X = Z = CH and Y = N).

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:365880 CAPLUS
DN 134:366795
TI DNA sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening
IN Sugiyama, Hiroshi; Saito, Akira; Iida, Hirokazu
PA Foundation for Scientific Technology Promotion, Japan
SO Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2001136974	A2	20010522	JP 1999-326007	19991116
	WO 2001036677	A1	20010525	WO 2000-JP7992	20001113
	W: US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
	EP 1152061	A1	20011107	EP 2000-974961	20001113
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 2003099998	A1	20030529	US 2002-285030	20021101
PRAI	JP 1999-326007	A	19991116		
	WO 2000-JP7992	W	20001113		
	US 2001-889379	A3	20010716		

AB Novel chemical species represented by the following general formula B-L-A (B = a chemical structure capable of recognizing the base sequence of DNA, for example, optionally substituted pyrrole-imidazole polyamide; A = a chemical structure capable of binding to unnatural nucleotide bases, for example, the alkylation moiety of duocarmycin A; L = a linker capable of binding the chemical structures A and B, for example, vinyl) and use of those compds. in screening of biol. activity of chemical compds. are disclosed. Those compds. are preferably DNA alkylating agents, applicable as anticancer agents. Reagent kits for screening, including microtiter plates, are claimed. Drug screening using human cancer cell lines, CL-wt cells, HLC-2 cells, Jurkat cells, and HeLa cells, and synthetic scheme for the bioactive compds., are described.

L4 ANSWER 15 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:327062 CAPLUS
DN 135:102536
TI Sequence-specific DNA interstrand cross-linking by imidazole-pyrrole CPI conjugate
AU Bando, Toshikazu; Iida, Hirokazu; Saito, Isao; Sugiyama, Hiroshi
CS CREST Japan Science and Technology Corporation (JST) Japan Division of Biofunctional Molecules Institute of Biomaterials and Bioengineering Tokyo Medical and Dental University, Kanda Chiyoda Tokyo, 101-0062, Japan
SO Journal of the American Chemical Society (2001), 123(21), 5158-5159
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society

DT Journal
LA English
AB DNA interstrand crosslinking inhibits both DNA replication and gene expression and therefore has considerable potential for mol. biol. and human medicine. However, an interstrand crosslinking agent that targets a predetd. base-pair sequence has not been achieved. Minor-groove binding polyamides that contain N-methylimidazole (Im)-N-methylpyrrole (Py)hydroxypyrrole (Hp), which uniquely recognize each of the four Watson-Crick base pairs, can be used as novel recognition parts of sequence-specific DNA alkylating agents. We also demonstrated that Im/Py diamide-CPI conjugate with a vinyl linker, ImPyLDu86, alkylates double-stranded DNA at predetd. sequences through highly cooperative homodimer formation. Herein we describe the synthesis of a covalent dimer of ImPyLDu86 connected with various linkers and their DNA interstrand crosslinking abilities. In conclusion, we developed a novel DNA interstrand crosslinking agent, that crosslinked double strands only in the presence of ImImPy at a nine-base-pair sequence, 5'-PyGGC(T/A)GCCPu-3'. The present system will provide a promising approach for the design of novel sequence-specific DNA interstrand crosslinking agents. Targeting specific sequences in the human genome by such sequence-specific crosslinking agent would constitute a powerful gene-regulating tool. Further studies on the applicability of this novel class of crosslinking agents are currently in progress.
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

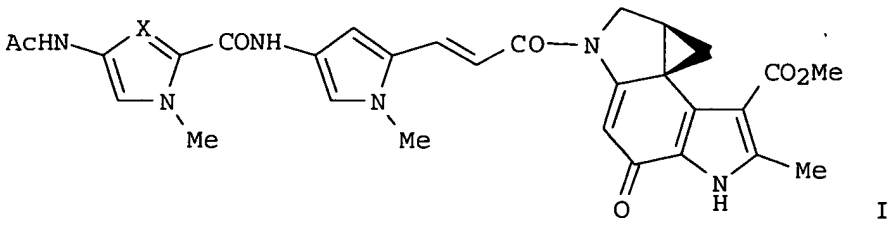
L4 ANSWER 16 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:341959 CAPLUS
DN 139:345455
TI Gene therapy·of cancer by using novel alkylating pyrrole-imidazole polyamide
AU Sugiyama, Hiroshi
CS Dep. of Biomaterials, Tokyo Medical and Dental University, Japan
SO Ikagaku Oyo Kenkyu Zaidan Kenkyu Hokoku (2001), Volume Date 2000, 19, 198-202
CODEN: IOKHEP; ISSN: 0914-5117
PB Ikagaku Oyo Kenkyu Zaidan
DT Journal
LA Japanese
AB Novel alkylating pyrrole-imidazole polyamide derivs. were design and prepared for gene therapy of cancer. The antitumor activities of the derivs. against Hela cells were tested.

L4 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:707167 CAPLUS
DN 133:266852
TI Preparation of duocarmycin derivatives capable of cleaving double-stranded DNA and method of utilization of the same
IN Sugiyama, Hiroshi; Tao, Zhi-Fu; Saito, Isao
PA Japan Science and Technology Corporation, Japan
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000058312	A1	20001005	WO 2000-JP1461	20000310
	W: CA, KR, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	JP 2000281679	A2	20001010	JP 1999-83591	19990326
	CA 2328903	AA	20001005	CA 2000-2328903	20000310
	EP 1083177	A1	20010314	EP 2000-907992	20000310
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 6713633	B1	20040330	US 2001-701264	20010808
PRAI	JP 1999-83591	A	19990326		

WO 2000-JP1461 W 20000310

GI



I

AB Novel chemical species represented by the following general formula B-L-A (I; wherein B represents a chemical structure capable of recognizing the base sequence of DNA, for example, optionally substituted pyrrole-imidazole polyamide; A represents a chemical structure capable of binding to one base of DNA, for example, the alkylation moiety of duocarmycin A; and L represents a linker capable of binding the chemical structures A and B, for example, vinyl) are prepared Also claimed are a method for alkylating DNA and a method for cleaving double-stranded DNA by using these compds.; and medicinal compns. with the use of these compds. for treatment of cancer. These compds. I, e.g. duocarmycin derivs. (II; R = CH, N) (preparation given) which recognizes base sequences TGACG or CGACG or their complimentary chain, are capable of simultaneously alkylating double-stranded DNA and cleaving the same and useful as artificial restriction enzymes or for targeting specific DNA base sequences for gene therapy. II (R = CH), II (R = N), and duocarmycin A in vitro showed IC50 of 1.5, 0.7 nM, and 4.7, resp., for inhibiting the proliferation of HeLaS3 cells.

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

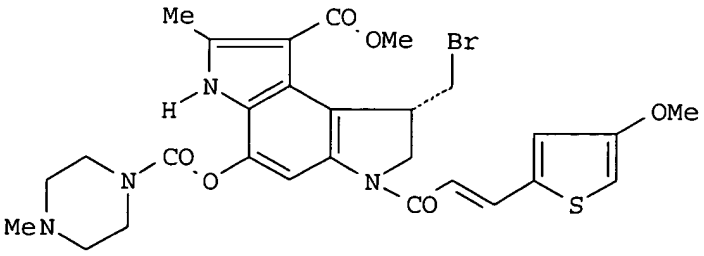
L4 ANSWER 18 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:488720 CAPLUS
DN 133:266627
TI Synthesis and antitumor activity of duocarmycin derivatives: A-ring pyrrole compounds bearing β-(5',6',7'-trimethoxy-2'-indolyl)acryloyl group
AU Amishiro, N.; Nagamura, S.; Kobayashi, E.; Okamoto, A.; Gomi, K.; Okabe, M.; Saito, H.
CS Pharmaceutical Research Institute, Kyowa Hakko Kogyo Company, Ltd., Shizuoka, 411-8731, Japan
SO Bioorganic & Medicinal Chemistry (2000), 8(7), 1637-1643
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
AB A series of A-ring pyrrole derivs. of duocarmycin bearing the β-(5',6',7'-trimethoxy-2'-indolyl)acryloyl group were synthesized, and evaluated for in vitro anticellular activity against HeLa S3 cells and in vivo antitumor activity against murine sarcoma 180 in mice. New Seg-B analogs bearing the β-(5',6',7'-trimethoxy-2'-indolyl)acryloyl group containing a double bond as a spacer had lower peripheral blood toxicity than the derivs. bearing the 5',6',7'-trimethoxyindole-2'-carboxyl group in Seg-B of the natural type. Moreover, most of them exhibited potent antitumor activity against in vivo murine tumor models.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:96276 CAPLUS
DN 132:275556
TI Highly cooperative DNA dialkylation by the homodimer of imidazole-pyrrole diamide-CPI conjugate with vinyl linker
AU Tao, Zhi-Fu; Saito, Isao; Sugiyama, Hiroshi
CS CREST, Japan Science and Technology Corporation (JST), Japan

SO Journal of the American Chemical Society (2000), 122(8), 1602-1608
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
OS CASREACT 132:275556
AB We synthesized new type of diamide-CPI conjugate possessing a vinyl linker (7). Sequence-selective alkylation of double-stranded DNA by 7 was investigated by high-resolution denaturing gel electrophoresis using .apprx.400 bp DNA fragments. Highly efficient alkylation predominantly occurs simultaneously at the purines of 5'-PyG(A/T)CPu-3' site on both strands at a nanomolar concentration of 7. These results suggest that the homodimer of conjugate 7 dialkylates both strands according to Dervan's pairing rule together with a new mode of recognition in which the Im-vinyl linker (L) pair targets G/C base pairs. In addition to the major dialkylation sites, a minor alkylation site was also observed at 5'-GT(A/T)GC-3'. This alkylation can be explained by an analogous slipped homodimer recognition mode in which the L-L pair recognizes the A/T base pair. Efficient dialkylation by the homodimer of 7 was further confirmed using oligonucleotides (ODNs). HPLC anal. revealed that the conjugate 7 simultaneously alkylates GN3/AN3 of the target sequences on both strands of ODNs.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:674932 CAPLUS
DN 132:22791
TI Synthesis and antitumor activity of duocarmycin derivatives: a-ring pyrrole compounds bearing 5-membered heteroarylacryloyl groups
AU Amishiro, Nobuyoshi; Nagamura, Satoru; Kobayashi, Eiji; Okamoto, Akihiko; Gomi, Katsushige; Saito, Hiromitsu
CS Pharmaceutical Research Institute, Kyowa Hakko Kogyo Company, Ltd., Shizuoka, 411-8731, Japan
SO Chemical & Pharmaceutical Bulletin (1999), 47(10), 1393-1403
CODEN: CPBTAL; ISSN: 0009-2363
PB Pharmaceutical Society of Japan
DT Journal
LA English
OS CASREACT 132:22791
GI



I

AB A series of A-ring pyrrole compds. of duocarmycin bearing 5-membered heteroarylacryloyl groups (thienylacryloyl and pyrrolylacryloyl) and heteroarylcarbonyl groups were synthesized and evaluated for in vitro anticellular activity against HeLa S3 cells and in vivo antitumor activity against murine sarcoma 180 in mice. Most of the thienylacrylates displayed in vitro anticellular activity equivalent to 4'-methoxycinnamates. Among the 8-O-[(N-methylpiperazinyl)carbonyl] derivs. of methoxy-thienylacrylates, compound I, having 4'-methoxy-2'-thienylacryloyl as segment-B (Seg-B), showed remarkably potent antitumor activity and low peripheral blood toxicity in vivo, which were equal to those of 8-O-[(N-methylpiperazinyl)carbonyl] derivs. of 4'-methoxycinnamates, compared with the A-ring pyrrole derivs. having the trimethoxyindole skeleton in Seg-B. On the other hand, the 2'-pyrrolylacrylates having a

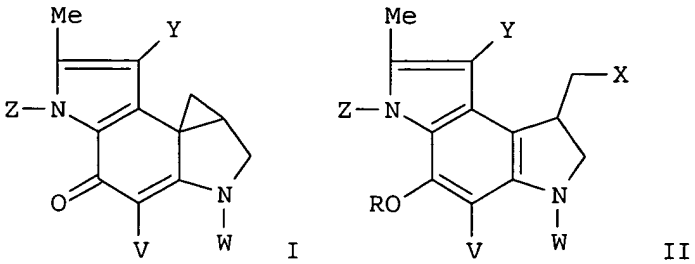
double bond as spacer showed 102- to 103-fold stronger anticellular activity than 2'-pyrrolecarboxylates (IC50<0.3 nM, 72h-exposure). The 8-O-acetate and 8-O-[(N-methylpiperazinyl)carbonyl] derivs. of 2'-pyrrolylacrylates exhibited an antitumor effect at a lower dose compared with the 8-O-[(N-methylpiperazinyl)carbonyl] derivs. with a 4'-methoxycinnamoyl moiety. Moreover, it was expected that the antitumor activity would be increased by the strength of the extra hydrogen bond formed between the nitrogen of the pyrrole amido group and DNA, owing to the increase of the number of N-methyl-2'-pyrrolecarboxamide units. However, 2'-pyrrolylacrylates having three N-methyl-2'-pyrrolecarboxamide units showed nearly equal antitumor activity to 2'-pyrrolylacrylates having only one N-methyl-2'-pyrrolecarboxamide unit.

RE.CNT 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:175925 CAPLUS
DN 128:243875
TI Preparation of antitumor DC-89 derivatives
IN Amishiro, Nobuyoshi; Saito, Hiromitsu; Okamoto, Akihiko; Okabe, Masami
PA Kyowa Hakko Kogyo Co., Ltd., Japan
SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

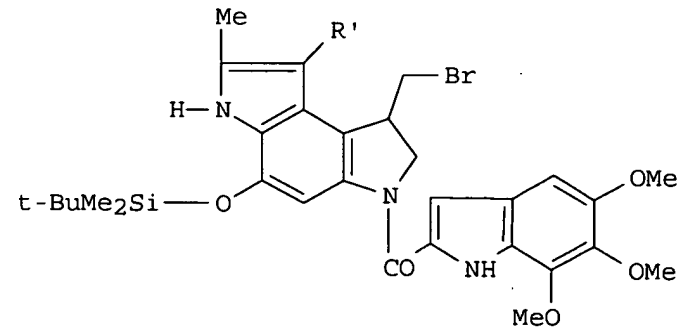
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9809966	A1	19980312	WO 1997-JP3089	19970903
	W: AU, BG, BR, CA, CN, CZ, HU, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9741345	A1	19980326	AU 1997-41345	19970903
PRAI	JP 1996-232723	A	19960903		
	WO 1997-JP3089	W	19970903		

OS MARPAT 128:243875
GI



I

II



III

AB DC-89 derivs. I and II [Y = H, halo, (un)substituted alkyl, COR1, OR2, SR3, etc.; R1 = H, (un)substituted alkyl, (un)substituted aralkyl, etc.;

R2 = H, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted aryl, etc.; R3 = H, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted aryl, (un)substituted heterocyclyl; W = H, acyl such as substituted acryloyl, etc.; Z = H, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted aryl, COR9 , etc.; R9 = H, acyl, silyl; V = H, halo, NO2, etc.; X = Cl, Br; R = H, OH, alkoxy, aryl, etc.] and their pharmaceutically acceptable salts are prepared E.g., the title compound III [R' = Me] was prepared in 56% yield by reduction of III [R' = COOMe] with DIBAL-H in THF. In an in vitro study, II [Y = CH2NMe2, R = V = Z = H, X = Cl, W = 5,6,7-trimethoxy-1H-indol-2-ylcarbonyl] HCl (also prepared) had an IC50 of 0.28 nM against HeLaS3 tumor cells.

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:87732 CAPLUS
DN 128:154100
TI Preparation of DC-89 derivatives as antitumor agents
IN Amishiro, Nobuyoshi; Saito, Hiromitsu; Okamoto, Akihiko; Gomi, Katsushige; Okabe, Masami
PA Kyowa Hakko Kogyo Co., Ltd., Japan
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9803509	A1	19980129	WO 1997-JP2516	19970722
	W: AU, BG, BR, CA, CN, CZ, HU, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9734631	A1	19980210	AU 1997-34631	19970722
PRAI	JP 1996-192634	A	19960723		
	WO 1997-JP2516	W	19970722		

OS MARPAT 128:154100
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. (I) wherein (II) represents (III) or (IV) [X = Cl, Br; R = H, COR1, etc.; R1 = H, (un)substituted alkyl, etc.], and W represents (V) or (VI) (Y1, Y2 = O, S, etc.; Q1-Q5 = H, alkoxy, NO2, etc.; m = 0-1; n = 0-2), are prepared I are useful as antitumor agents. Compound (VII) was treated with NaH and then reacted with compound (VIII) to give 73% the title compound (IX), which showed IC50 of 2.9 nM against HeLaS3 cell.

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

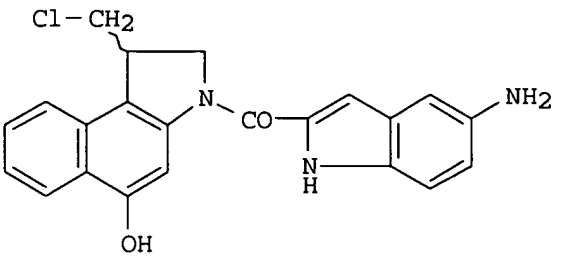
L4 ANSWER 23 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:783786 CAPLUS
DN 128:48468
TI Preparation of DNA-binding glucuronide indoles immuno-conjugates as antitumors
IN Wang, Yuqiang; Wright, Susan C.; Larrick, James W.
PA Panorama Research, Inc., USA
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9744000	A2	19971127	WO 1997-US9055	19970522
	WO 9744000	A3	19971231		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	US 5843937	A	19981201	US 1996-652883	19960523
	AU 9732170	A1	19971209	AU 1997-32170	19970522
	EP 918752	A2	19990602	EP 1997-927798	19970522
	R: AT, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE				
	CN 1219841	A	19990616	CN 1997-194862	19970522
	JP 2000511893	T2	20000912	JP 1997-542898	19970522
PRAI	US 1996-652883	A	19960523		
	WO 1997-US9055	W	19970522		

OS MARPAT 128:48468
GI



I

AB The present invention relates to novel DNA alkylating agents and the prodrugs of these agents which are useful as antitumors and DNA labeling agents. The compds. are hydroxydihydrobenzindole oligopeptides and prodrugs thereof wherein the monomeric constituents are derived from monocyclic, or bicyclic heterocyclic aromatic residues. Thus, indole I was prepared and tested for its antitumor activity with cytotoxicity (IC50 = 0.09 nM).

L4 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:248963 CAPLUS
DN 125:11480
TI Cyclopropapyrroloindole-oligopeptide anticancer agents
IN Lown, J. William; Wang, Yuqiang; Luo, Weide
PA Synphar Laboratories, Inc., Can.
SO U.S., 17 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5502068	A	19960326	US 1995-381355	19950131
	CA 2210093	AA	19960808	CA 1996-2210093	19960131
	WO 9623497	A1	19960808	WO 1996-US727	19960131
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE				
	AU 9649643	A1	19960821	AU 1996-49643	19960131
	AU 698001	B2	19981022		
	EP 800390	A1	19971015	EP 1996-906176	19960131
	EP 800390	B1	20021204		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	JP 11500427	T2	19990112	JP 1996-523576	19960131

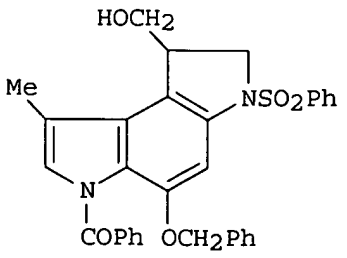
	AT 228837	E	20021215	AT 1996-906176	19960131
PRAI	US 1995-381355	A	19950131		
	WO 1996-US727	W	19960131		

OS MARPAT 125:11480
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention is directed to novel cyclopropylpyrroloindole-oligopeptide compds. which are useful as anticancer agents. The novel cyclopropylpyrroloindole-oligopeptide compds. have the following general structure: I wherein, Het1 and Het2 are individually selected from the group consisting of pyrrole, imidazole, N-alkylimidazole, N-alkoxymethylimidazole, thiophene, thiophene, furan, thiazole, oxazole, N-alkylpyrrole, N-alkoxymethylpyrrole and pyrazole, R is selected from the group consisting of a valence bond; a divalent C1-C6 alkyl; a divalent C2-C6 alkenyl; a divalent C2-C6 alkynyl; a divalent cycloalkane of formula CpH2p-2 wherein p is 3 to 7; and an ortho, meta or para linked aromatic group, A is selected from the group consisting of a C1-C6 alkyl group; an amidine or derivative thereof; a guanidine; a secondary, tertiary or quaternary ammonium salt; and a sulfonium salt, n is 0 to 3, and m is 0 to 3, wherein when n=0, m is 1-3. Thus, e.g., deprotection of 5-benzyloxy-3-tert-butyloxycarbonyl-1-chloromethyl-8-methyl-1,2-dihydro-3H-pyrrolo[3,2-e]lindole (II) followed by coupling with 4-(4-butyramido-N-methyl-2-pyrrolecarboxyamido)-N-methyl-2-pyrroleacrylic acid and ring closure afforded (E)-1,2,8,8a-tetrahydro-7-methyl-2-[4-(4-butyramido-N-methyl-2-pyrrolecarboxyamido)-N-methyl-2-pyrroleacryloyl]cyclopropa[c]pyrrolo[3,2-e]indole-4-(5H)-one [(E)-III] which exhibited cytotoxicity of TD50 = 9.50 + 10-10 μg/mL for KB human nasopharyngeal tumor cells (TD50 = 1 + 10-6 μg/mL for CC-1065). A detailed anal. of the frequency of occurrence of bases flanking the prominent DNA alkylation sites for III is given and compared with CC-1065, providing evidence of the main cellular event that gives rise to the expression of anticancer properties of the new drugs and how they differ in detail from CC-1065.

L4 ANSWER 25 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:441562 CAPLUS
DN 125:167628
TI Enzymic preparation of optically active precursors of CPI, the DNA alkylation subunit of the naturally occurring antitumor antibiotic CC-1065
AU Ling, Lei; Lown, J. William
CS Department Chemistry, University Alberta, Edmonton, T6G 2G2, Can.
SO Chemical Communications (Cambridge) (1996), (13), 1559-1560
CODEN: CHCOFS; ISSN: 1359-7345
PB Royal Society of Chemistry
DT Journal
LA English
GI



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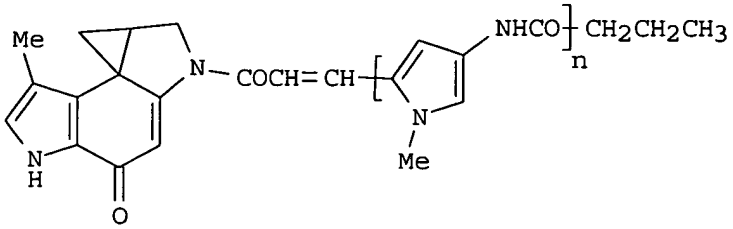
AB Some immediate precursors of CPI were subjected to enzymic resolution with lipase PS in vinyl acetate; racemic pyrroloindole I was effectively resolved by two consecutive enzymic reactions.

L4 ANSWER 26 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:185423 CAPLUS
DN 124:278276
TI Design, synthesis, cytotoxic properties and preliminary DNA sequencing evaluation of CPI-N-methylpyrrole hybrids. Enhancing effect of a trans double bond linker and role of the terminal amide functionality on cytotoxic potency
AU Wang, Yuqiang; Gupta, Rajan; Huang, Liren; Luo, Weide; Lown, J. William
CS Dep. of Chemistry, Univ. of Alberta, Edmonton, AB, T6G 2G2, Can.
SO Anti-Cancer Drug Design (1996), 11(1), 15-34
CODEN: ACDDEA; ISSN: 0266-9536
PB Oxford University Press
DT Journal
LA English
AB In an approach to the design and exploration of the properties of cyclopropylindole (CPI)-lexitropsin conjugates as potential anticancer agents, CPI-N-methylpyrroles of two sep. classes have been synthesized and characterized. These comprise structures (i) in which the N-methylpyrrole moiety bears amide groups of different sizes and (ii) in which both flexible and rigid linkers are introduced between the CPI and N-methylpyrrole units. The extent and the relative rates of DNA cleavage following alkylation and thermal treatment by these CPI conjugates were determined by an agarose gel mobility shift assay. The DNA sequence preferences of the 7 new agents were also determined in a preliminary study by high-resolution polyacrylamide gel electrophoresis and contrasted with that of CC-1065. The CPI-N-methylpyrrole agents avoid the major alkylation sites of CC-1065, but all alkylate the minor CC-1065 site of 5'AATA and exhibit a consensus sequence of 5'-N.A/T.A/T.A. The cytotoxicities of these compds. were determined against KB human tumor cells in vitro. Compound 6, bearing a 4-butyramide group in the N-methylpyrrole, is 100 times more potent than 7 which lacks an amide group, while 10 which bears a rigid trans double bond linker is 100 times more potent than its flexible ethyl-linked counterpart.

L4 ANSWER 27 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:751030 CAPLUS
DN 123:217829
TI Characterization of a CPI-Lexitropsin Conjugate-Oligonucleotide Covalent Complex by 1H NMR and Restrained Molecular Dynamics Simulation
AU Fregeau, Nancy L.; Wang, Yuqiang; Pon, Richard T.; Wylie, William A.; Lown, J. William
CS Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2, Can.
SO Journal of the American Chemical Society (1995), 117(35), 8917-25
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
GI



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AB The structural features of the covalent bonding of a novel CPI (cyclopropylpyrroloindole)-lexitropsin conjugate (I) to a model duplex DNA has been examined by high field 1H-NMR analyses and restrained mol. dynamics calcns. I, that was designed for enhanced DNA binding compared with natural (+)CC-1065, exhibits an exceptional cytotoxic potency against KB

human nasopharangeal tumor cells in vitro of IC50 = 0.76 fg/L. Racemic I reacted readily with the duplex oligodeoxyribonucleotide d(CGCAATTGCG)2 to form a single covalent adduct. The latter exhibits a new absorption band at 396 nm characteristic of the bound drug in addition to the duplex absorption at 258 nm. 1H-NMR anal. confirms by selective chemical shift changes and NOEs between protons in the drug and in the duplex that covalent bonding has taken place at A4. The drug is aligned in a 5'- to 3'-direction at the AATT core in the minor groove resulting from the selective binding of one enantiomer of I and corresponding to the mode of binding of (-)-CC-1065. The stereochem. at the site of attachment at the 4a position of the drug is (S), an inference that is corroborated by the restrained mol. dynamics simulation. The latter computations predict average total energies for the (R) and (S) drug-DNA adducts of +42 and -0.42 kcal/mol, resp., signifying substantially greater stability for the latter diastereomer. The covalent adduct appears to be quite stable and showed no sign of reversibility such as has been observed with other CPI-based agents which may tentatively be attributed to the exceptionally snug fit of all parts of the drug within the minor groove.

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